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(54) Quinoline and quinazoline compounds useful in therapy

Chinoline und Chinazoline Verbindungen und ihre therapeutische Anwendung

Composés de quinoléine et quinazoline et leur utilisation en thérapeutique

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EP 0 875 506 B1

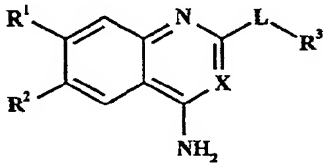
Description

[0001] This invention relates to novel compounds useful in therapy, particularly in the treatment of benign prostatic hyperplasia.

[0002] International Patent Application WO 89/05297 discloses a number of substituted quinazoline compounds that are indicated as inhibitors of gastric acid secretion.

[0003] WO 92/00073 discloses R(+)-terazosin and its use in the treatment of benign prostatic hyperplasia.

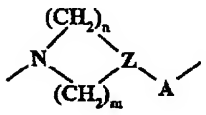
[0004] According to the present invention, there is provided a compound of formula I,



I

wherein

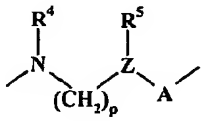
R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;
R^2 represents Phenyl, naphthyl, or an aromatic heterocycle having 5 or 6 ring members, at least one of which is N,O or S, optionally substituted by C_{1-4} alkyl or SO_2NH_2;
R^3 represents a 4-, 5-, 6-, or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by one or two oxygen atoms;
X represents CH or N; and
L is absent,
or represents a cyclic group of formula Ia,



Ia

in which A is attached to R^3;
A represents CO or SO_2;
Z represents CH or N;
m represents 1 or 2, and in addition, when Z represents CH, it may represent 0; and
n represents 1, 2 or 3, provided that the sum of m and n is 2, 3, 4 or 5;

or represents a chain of formula Ib,



Ib

in which A is attached to R^3;
A and Z are as defined above;
R^4 and R^5 independently represent H or C_{1-4} alkyl; and
p represents 1, 2 or 3, and in addition, when Z represents CH, it may represent 0;

or a pharmaceutically acceptable salt thereof (referred to together herein as "the compounds of the invention").

[0005] Pharmaceutically acceptable salts include acid addition salts, such as hydrochloride and hydrobromide salts, and phosphate salts.

[0006] Alkyl or alkoxy groups that R^{1-5} may represent or include can be straight chain, branched chain, cyclic, or a combination thereof.

[0007] "Aromatic heterocycle" in the definition of R^2 includes for example pyridinyl or furanyl.

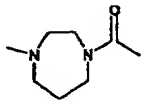
[0008] Preferably, heterocyclic rings represented or comprised by R^3 are saturated. Examples include morpholine, thiomorpholine-1,1-dioxide, 1,4-dioxan, tetrahydrofuran and piperidine.

[0009] The compounds of the invention may be optically active. The invention includes all optical isomers of the compounds of formula I, and all diastereoisomers thereof.

[0010] The compounds of the invention may exist in a number of tautomeric forms. The invention includes all such tautomeric forms.

[0011] Preferred groups of compounds that may be mentioned include those in which:

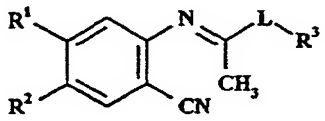
(a) R^1 represents methoxy;
(b) R^2 represents phenyl or 2-pyridinyl;
(c) R^3 represents morpholinyl, or a piperidine ring which is fused to a benzene or pyridine ring;
(d) L is absent or represents 1,4-diazepanylcarbonyl-



and
(e) L is absent and R^3 represents a piperidine ring fused to a benzene ring which is substituted by $NHSO_2(C_{1-4}$ alkyl).

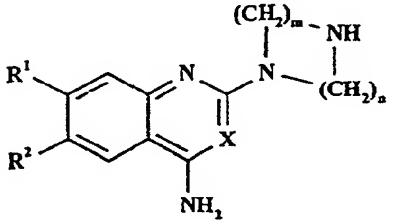
[0012] According to the invention, there is also provided a process for the production of a compound of the invention, which comprises:

(a) when X represents CH, cyclizing a compound of formula II,

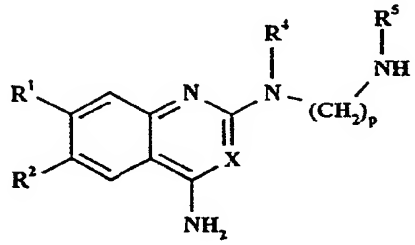


II

in which R^{1-3} and L are as defined above; or
(b) when Z represents N, reacting a compound of formula IIIa or IIIb, as appropriate,



IIIa

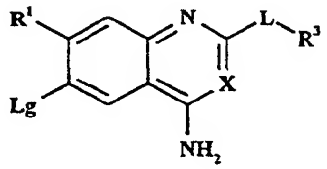


IIIb

in which R^1, R^2, R^4, R^5, X, m, n and p are as defined above, with a compound of formula IV,

$$Lg\text{-}A\text{-}R^3 \qquad IV$$

in which R^3 is as defined above, A represents CO or SO2 and Lg represents a leaving group; or
(c) reacting a compound of formula V,

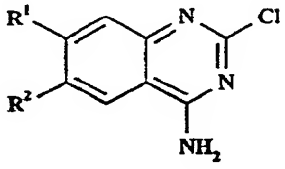


V

in which R^1, R^3, X and L are as defined above, and Lg is a leaving group, with a compound of formula VI,

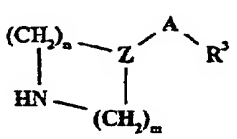
R^2-M VI

in which R^2 is as defined above and M represents substituted boron, zinc or tin, in the presence of a palladium catalyst; or
(d) when X represents N, reacting a compound of formula VII,

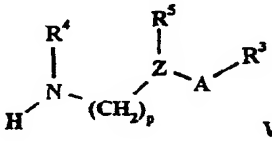


VII

in which R^1 and R^2 are as defined above, with a compound of formula VIIIa, VIIIb or VIIIc, as appropriate,



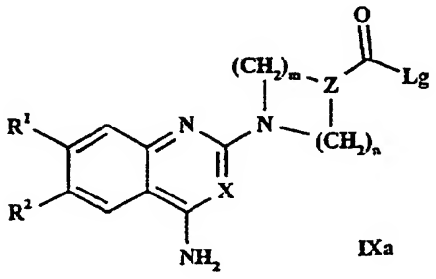
VIIIa,



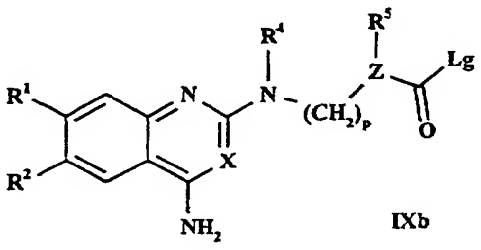
VIIIb,

HR^{3a} VIIIc

in which R^{3-5}, A, Z, m, n and p are as defined above; and R^{3a} has the same significance as R^3 above except that it contains a nucleophilic nitrogen atom in the heterocyclic ring which is attached to the H in formula VTIIc; or
(e) when A represents CO and R^3 comprises a nucleophilic nitrogen atom in the heterocyclic ring attached to L, reacting a compound of formula IXa or IXb, as appropriate,



IXa



IXb

in which R^1, R^2, R^4, R^5, X, Z, m, n and p are as defined above, and Lg is a leaving group, with a compound of

formula VIIIc, as defined above; or

(f) conversion of a compound of formula I in which L represents a cyclic group of formula Ia, to a corresponding compound of formula I in which L represents a chain of formula Ib in which R^4 and R^5 each represent H, by the action of a strong base;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable salt or vice versa.

[0013] In process (a), the cyclization may be carried out in the presence of a strong base (for example lithium diisopropylamide) in a solvent that does not adversely affect the reaction (for example tetrahydrofuran), around room temperature. Alternatively, it may be performed using potassium hydroxide in a solvent which does not adversely affect the reaction (for example dimethylsulphoxide), at the reflux temperature of the solvent.

[0014] In process (b), suitable leaving groups are OH and Cl. When the compound of formula IV is a carboxylic acid, the reaction may be carried out in the presence of conventional coupling agents [for example 1-hydroxybenzotriazole monohydrate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 4-methylmorpholine] in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) at or around room temperature. When the leaving group is Cl, the reaction may be carried out in a solvent which does not adversely affect the reaction (for example CH_2Cl_2 or tetrahydrofuran), around 0°C or up to the reflux temperature of the solvent.

[0015] In process (c), suitable leaving groups include the trifluoromethylsulphonate (triflate) group. The palladium catalyst may be tetrakis(triphenylphosphine)palladium(0). M may be $B(OH)_2$, $B(CH_2CH_2)_2$, $Sn(CH_2CH_2CH_2CH_3)_3$, $Sn(CH_3)_3$ or ZnCl. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example, when M is $B(OH)_2$, a mixture of toluene, ethanol and 1M aqueous sodium carbonate) at an elevated temperature (for example the reflux temperature of the solvent).

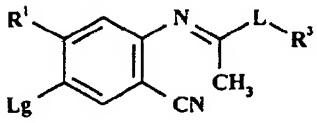
[0016] In process (d), the reaction may be carried out in a solvent which does not adversely affect the reaction (for example n-butanol) in the presence of a base (for example triethylamine) at an elevated temperature (for example 100°C).

[0017] In process (e), suitable leaving groups include Cl. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example THF) in the presence of a base (for example triethylamine) at room temperature.

[0018] The reaction may also be carried out without isolating the compound of formula IXa or IXb, by reacting a compound of formula IIIa or IIIb with triphosgene and a compound of formula VIIIc. In this case the leaving group is -Cl. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example CH_2Cl_2) in the presence of a base (for example triethylamine) at or around room temperature.

[0019] In process (f), suitable strong bases include lithium diisopropylamide. The reaction may be carried out in a solvent that does not adversely affect the reaction (for example THF).

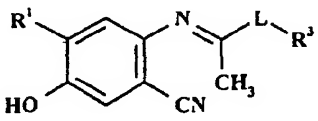
[0020] Compounds of formula II [see process (a)] may be prepared by reaction of a compound of formula X,



X

in which R^1, R^3 and L are as defined above and Lg is a leaving group (such as a triflate group), with a compound of formula VI, as defined above, using the conditions described for process (c) above.

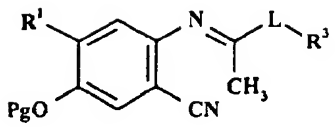
[0021] Compounds of formula X may be prepared by converting the OH group in a compound of formula XI,



XI

in which R^1, R^3 and L are as defined above, into a leaving group (such as a triflate), for example by reaction with triflic anhydride. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) in the presence of pyridine, below room temperature (for example -20°C).

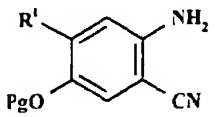
[0022] Compounds of formula XI may be prepared by deprotecting a compound of formula XII,



XII

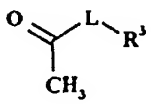
in which R^1, R^3 and L are as defined above and Pg is a hydroxy protecting group (such as benzyl). When Pg is benzyl, the deprotection may be achieved by hydrogenation over palladium-on-charcoal, in ethanol, around room temperature.

[0023] Compounds of formula XII may be prepared by reaction of a compound of formula XIII,



XIII

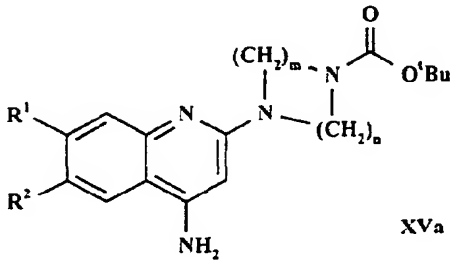
in which R^1 and Pg are as defined above, with a combination of a compound of formula XIV,



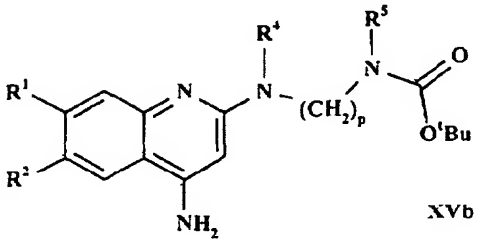
XIV

in which R^3 and L are as defined above, and phosphorous oxychloride in dichloromethane at the reflux temperature of the solvent.

[0024] Compounds of formula IIIa or IIIb [see process (b)] in which X represents CH may be prepared from compounds of formula XVa or XVb, as appropriate,



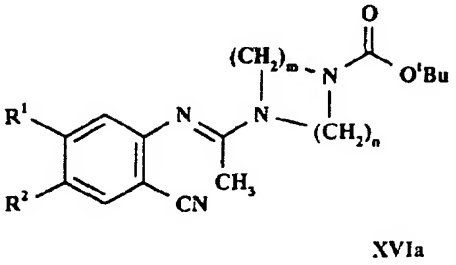
XVa



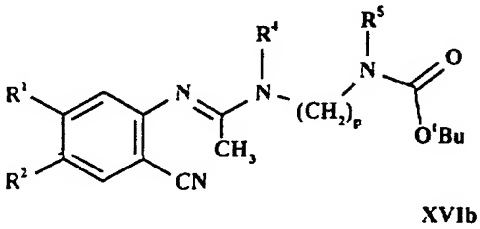
XVb

in which R^1, R^2, R^4, R^5, m, n and p are as defined above, by bubbling HCl gas through a solution of the compound in dichloromethane.

[0025] Compounds of formula XVa or XVb may be prepared from compounds of formula XVIa or XVIb, as appropriate,



XVIa

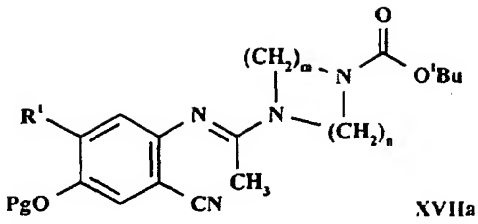


XVIb

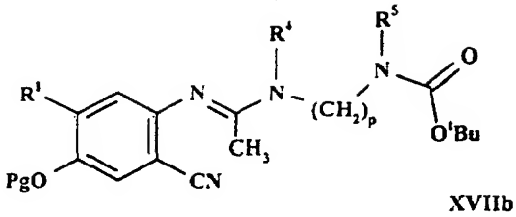
in which R^1, R^2, R^4, R^5, m, n and p are as defined above, by cyclization using potassium hydroxide or lithium diisopropylamide at an elevated temperature (such as 90°C) in DMSO, quenching with water.

[0026] Compounds of formula XVIa or XVIb may be prepared from compounds of formula XVIIa or XVIIb, as appro-

priate,



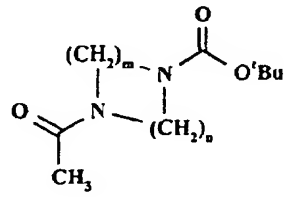
XVIIa



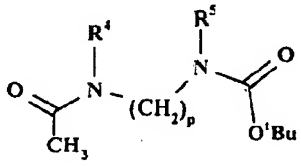
XVIIb

in which R^1, R^4, R^5, m, n and p are as defined above, and Pg is a hydroxy protecting group, by reaction with a compound of formula VI, as defined above, using the conditions described for process (c) above.

[0027] Compounds of formula XVIIa or XVIIb may be prepared by reacting a compound of formula XIII, as defined above, with a compound of formula XVIIIa or XVIIIb, as appropriate,



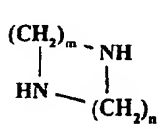
XVIIIa



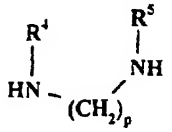
XVIIIb

in which R^4, R^5, m, n and p are as defined above, by the method described above for producing compounds of formula XII.

[0028] Compounds of formula IIIa or IIIb [(see process (b)] in which X represents N may be prepared by reacting a compound of formula VII, as defined above, with a compound of formula XIXa or XIXb, as appropriate,



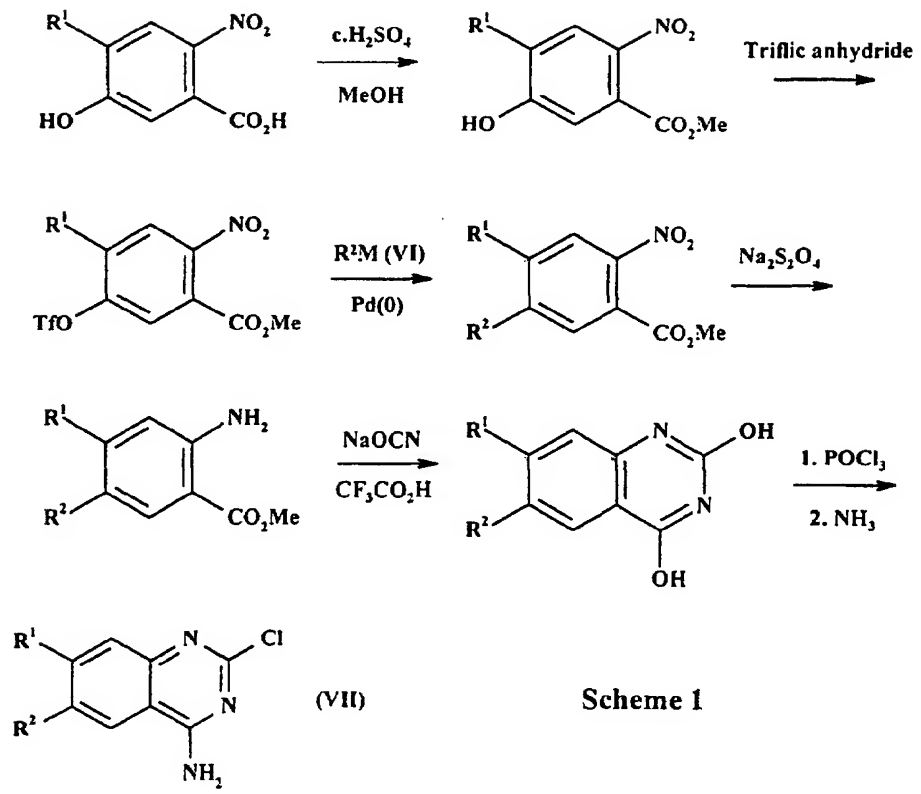
XIXa



XIXb

in which R^4, R^5, m, n and p are as defined above, using the conditions mentioned for process (d) above.

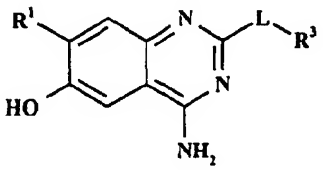
[0029] Compounds of formula VII may be prepared by conventional means from known compounds (or compounds available using known techniques) according to Scheme 1 below (see also Example 1), in which R^1, R^2 and M are as defined above:



Scheme 1

[0030] Compounds of formula V [see process (c)] in which X represents CH may be prepared by cyclization of a compound of formula X, as defined above, using the reaction conditions mentioned in process (a) above.

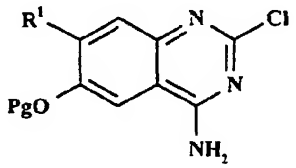
[0031] Compounds of formula V in which X represents N may be prepared by converting the OH group in a compound of formula XX,



XX

in which R^1, R^3 and L are as defined above, into a leaving group (such as a triflate group), for example by reaction with triflic anhydride.

[0032] Compounds of formula XX may be prepared from compounds of formula XXI,

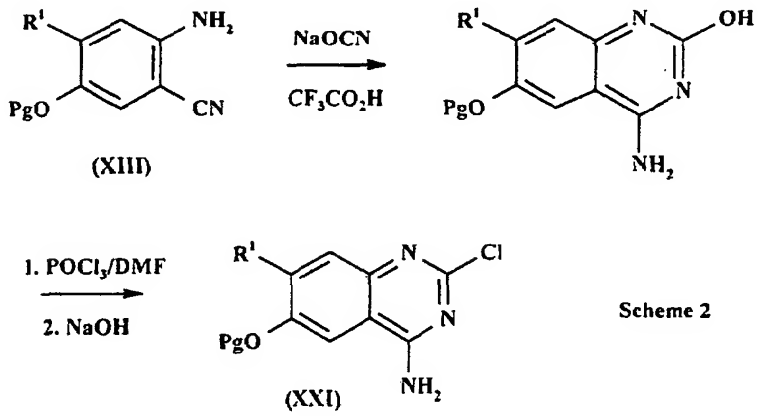


XXI

in which R^1 and Pg are as defined above, by reaction with a compound of formula VIIIa, VIIIb or VIIIc, as defined above, as appropriate, using the conditions described in process (d).

[0033] Compounds of formula XXI may be prepared from compounds of formula XIII, as defined above, by conven-

tional means according to Scheme 2 below (see also Example 11) in which R^1 and Pg are as defined above:



Scheme 2

[0034] The preparation of compounds of formula VII {see process (d)] has already been described above.

[0035] Compounds of formula VIIIa and VIIIb may be prepared by reaction of a compound of formula IV, as defined above, with a compound of formula XIXa or XIXb, as defined above, as appropriate, using the conditions indicated for process (d) above.

[0036] Compounds of formula IXa and IXb [see process (e)] in which Lg represents Cl may be prepared from compounds of formula IIIa or IIIb, as defined above, as appropriate, by reaction with triphosgene. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) in the presence of a base (for example triethylamine) at around -10°C.

[0037] Compounds of formulae IV, VI, VIIIc, XIII, XIV, XVIIIa, XVIIIb, XIXa and XIXb are either known or are available using known techniques.

[0038] The intermediate compounds of formulae II, IIIa, IIIb and VII, form a further aspect of the invention, together with compounds of formula V when Lg represents the triflate group, and compounds of formulae IXa and IXb when Lg represents chloro.

[0039] It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

[0040] The compounds of the invention are useful because they possess pharmacological activity in animals. In particular, the compounds are useful in the treatment of a number of conditions including hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia and benign prostatic hyperplasia. The latter condition is of greatest interest. Thus, according to another aspect of the invention, there is provided the use of the compounds of the invention as pharmaceuticals, and the use of the compounds of the invention in the manufacture of a medicament for the treatment of benign prostatic hyperplasia. The compounds of the invention may be administered by any convenient route, for example orally, parenterally (*e.g.* intravenously, transdermally) or rectally. The daily dose required will of course vary with the particular compound used, the particular condition being treated and with the severity of that condition. However, in general a total daily dose of from about 0.01 to 10mg/kg of body weight, and preferably about 0.05 to 1mg/kg, is suitable, administered from 1 to 4 times a day.

[0041] The compounds of the invention will generally be administered in the form of a suitable pharmaceutical formulation. Thus, according to another aspect of the invention, there is provided a pharmaceutical formulation including preferably less than 50% by weight of a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical formulation is preferably in unit dose form. Such forms include solid dosage forms, for example tablets, pills, capsules, powders, granules, and suppositories for oral, parenteral or rectal administration; and liquid dosage forms, for example sterile parenteral solutions or suspensions, suitably flavoured syrups, flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, and elixirs and similar pharmaceutical vehicles.

[0042] Solid formulations may be prepared by mixing the active ingredient with pharmaceutical carriers, for example conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and other diluents, for example water, to form a homogeneous preformulation formulation in which the active ingredient is uniformly dispersed so that it may be readily subdivided into equally effective

unit dosage forms containing typically from 0.1 to about 500mg of the active ingredient. The solid dosage forms may be coated or otherwise compounded to prolong the action of the formulation.

[0043] The formulations of the invention may also contain a human 5-α reductase inhibitory compound [see International Patent Application WO 95/28397], or a compound of the invention could be presented in a pharmaceutical pack also containing a human 5-α reductase inhibitory compound as a combined preparation for simultaneous, separate or sequential use.

[0044] The compounds of the invention may be tested in the screens set out below.

Contractile responses of human prostate

[0045] Prostatic tissue was cut into longitudinal strips (approximately 3x2x10 mm) and suspended in organ baths under a resting tension of 1 g in Krebs Ringer bicarbonate of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The solution also contained 10 mM cocaine and 10 mM corticosterone. Tissues were exposed to a sensitising dose of (-)-noradrenaline (100 mM) and washed over a 45 minute period. Isometric contractions were obtained in response to cumulative additions of (-)-noradrenaline to obtain control curves in all tissues. A further curve was then generated in the presence or absence of antagonist (incubated for 2 hours). Antagonist affinity estimates (pA_2) were determined using a single concentration of competing antagonist, pA_2 = -log [A]/(DR-1) where the dose ratio (DR), relative to corresponding controls, was produced by a single concentration of antagonist [A], assuming competitive antagonism and Schild regression close to unity.

Anaesthetised dog model of prostatic pressure and blood pressure

[0046] Mature male beagles (12-15 kg body weight) were anaesthetised with sodium pentobarbitone (30-50 mg/kg i.v.) and a tracheal cannula was inserted. Subsequent anaesthesia was maintained using pentobarbitone infusion. The animals were respirated with air using a Bird Mk8 respirator (Bird Corp., Palm Springs, CA, USA) adjusted to maintain blood gasses in the range pO_2 12-14.7 kPa (90-110 mm Hg), pCO_2 4.7-6 kPa (35-45 mm Hg), pH 7.35-7.45. Body temperature was maintained at 36-37.5°C using a heated operating table. Catheters were placed into the left femoral artery for recording blood pressure and into the left femoral vein for compound administration. Heart rate was recorded via the lead II E.C.G. A laparotomy was performed to cannulate both ureters to prevent change of fluid volume within the bladder. A 7F cardiac catheter (with a 1.5 ml capacity balloon tip) was inserted into the bladder via the urethra. The balloon was filled with air and the catheter withdrawn until the balloon became lodged in the prostate, which was confirmed by digital pressure. Balloon pressure was recorded via a Druck transducer. Prostatic pressure and haemodynamic parameters were made on a Grass Polygraph (Grass Instruments, Quincy, Mass, U.S.A.) and the data measured on line using a Motorola 68000-based microcomputer system (Motorola Inc., Temple, AZ, U.S.A.). Compounds were made up in PEG 300 and administered i.v. through a catheter in the femoral vein. Responses to phenylephrine (1-16 μg/kg i.v. in saline) were obtained to generate control dose-response curves (two control curves for each experiment). Compounds were administered (in terms of compound base) at 10-300 μg/kg i.v. 5 min before construction of phenylephrine curves (constructed up to a maximum dose of 128 μg/kg in the presence of test compound).

[0047] Due to α_1-related dysrhythymic properties of phenylephrine, absolute maximal responses were not obtained but were taken as 10 % greater than the control response obtained with 16 μg/kg phenylephrine. Drug concentrations were calculated on the basis of molar weight of compound/kg body weight thus allowing a "pseudo pA_2" calculation by Schild analysis using dose ratios derived from shifts in the phenylephrine dose-response curves.

[0048] The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective (in particular they may have beneficial effects in benign prostatic hyperplasia without causing undesirable cardiovascular effects, for example because they are able to selectively antagonise prostatic receptor subtypes of the α_1-adrenoceptor), or have other more useful properties than the compounds of the prior art.

[0049] The invention is illustrated by the following examples, in which the following abbreviations are used:

DMF = dimethylformamide
DMSO = dimethylsulphoxide
EtOAc = ethyl acetate
EtOH = ethanol
h = hour
MeOH = methanol
min = minute
n-BUOH = n-butanol

THF = tetrahydrofuran

Intermediate 1

1-(4-Morpholinecarbonyl)-1,4-diazepane hydrochloride

(a) 1-(t-Butyloxycarbonyl)-1,4-diazepane

[0050] To a solution of homopiperazine (100g, 1.0 mol) and triethylamine (210ml, 152g, 1.5mol) in CH_2Cl_2 (500ml) at 0°C was added a solution of di-(t-butyl) dicarbonate (195g, 0.89mol) in CH_2Cl_2 (300ml). The mixture was allowed to warm to room temperature and stirred for 18h after which time the CH_2Cl_2 was evaporated under reduced pressure. The resulting residue was partitioned between ether and 2N citric acid and the aqueous layer was extracted with ether (4x200ml). The aqueous layer was basified with 2N aqueous NaOH and then extracted with CH_2Cl_2 (4x400ml). The combined CH_2Cl_2 extracts were washed with H_2O (2x), saturated brine (1x) and dried over $MgSO_4$. Evaporation under reduced pressure followed by azeotroping with CH_2Cl_2 (4x) gave the subtitle compound as a yellow waxy solid (94.3g, 53%). R_f 0.25 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 201 (MH^+). Found: C,58.86; H,10.03; N,13.58; $C_{10}H_{20}N_2O_2$ 0.05.CH_2Cl_2 requires C, 59.02; H, 9.91; N,13.70%.

(b) 1-(t-Butyloxycarbonyl)-4-(4-morpholinecarbonyl)-1,4-diazepane

[0051] A solution of the compound of step (a) (92.0g, 0.46mol) and triethylamine (96.0ml, 69.7g, 0.69mol) in CH_2Cl_2 (500ml) at 0°C was treated dropwise with a solution of 4-morpholinecarbonyl chloride (64.0ml, 82.0g, 0.55mol) in CH_2Cl_2 (100ml) and the reaction was stirred at room temperature under N_2 for 18h. The reaction mixture was then diluted with CH_2Cl_2 (400ml) and washed with 2N citric acid (3x400ml), saturated brine (1x500ml), dried over $MgSO_4$ and evaporated to give the subtitle compound as an off-white solid (141.7g, 98%). R_f 0.80 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 314 (MH^+). Found: C,57.50; H,8.69; N.13.41; $C_{15}H_{27}N_3O_4$ requires C, 57.50; H, 8.69; N,13.41%.

(c) 1-(4-Morpholinecarbonyl)-1,4-diazepane hydrochloride

[0052] A solution of the compound of step (b) (140.0g, 0.44mol) in CH_2Cl_2/MeOH (1/1, v/v, 600ml) at 0°C was saturated with HCl gas and the reaction mixture was stirred at room temperature under N_2 for 18h after which time the reaction mixture was evaporated under reduced pressure and slurried in EtOAc to give, after filtration, a white hygroscopic solid. This was further purified by slurrying in acetone, filtering, washing with ether and drying under reduced pressure at 60°C to give the title compound as a colourless solid (99.0g, 90%). R_f 0.41 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 214 (MH^+). Found: C,47.50; H,8.10; N,16.55; $C_{10}H_{19}N_3O_2$ HCl 0.2.H_2O requires C, 47.41; H, 8.12; N, 16.59%.

Intermediate 2

1-Acetyl-4-(4-morpholinecarbonyl)-1,4-diazepane

[0053] To a solution of Intermediate 1 (50g, 0.2mol) and triethylamine (42ml, 30.5g, 0.3mol) in CH_2Cl_2 (400ml) at 5°C was added acetic anhydride (23ml, 24.9g, 0.24mol) dropwise over 15min and the reaction was then stirred for a further 2h at room temperature under N_2. Dilution with CH_2Cl_2 (600ml) was followed by washing with saturated aqueous sodium bicarbonate (2x200ml) and the combined aqueous layers extracted with CH_2Cl_2 (1x100ml). The CH_2Cl_2 layers were combined and washed with saturated brine, dried over $MgSO_4$ and evaporated to give a light brown oil. This was dissolved in CH_2Cl_2 (300ml) and treated with triethylamine (8ml, 5.8g, 0.06mol) and EtOH (5ml), stirred for 1h at room temperature then washed with saturated sodium bicarbonate and the aqueous layer extracted with CH_2Cl_2 (5x). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated under reduced pressure to give a yellow oil that was then azeotroped with CH_2Cl_2 (4x) to give the title compound as a yellow oil (47.1g, 92%). R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 256 (MH^+). Found: C,52.62; H,8.18; N,15.02; $C_{12}H_{21}N_3O_3$ 0.3.CH_2Cl_2 requires C, 52.61; H. 7.75; N,14.96%.

Intermediate 3

1-(4-Morpholinesulphonyl)-1,4-diazepane hydrochloride

(a) 1-(t-Butyloxycarbonyl)-4-{4-morpholinesulphonyl}-1,4-diazepane

[0054] The subtitle compound was prepared by the method of Intermediate 1(b) from the compound of Intermediate 1(a) and 4-morpholinesulphonyl chloride [Repine *et al*, J. Med. Chem., 34, 1935 (1991)]. The reaction mixture was partitioned between CH_2Cl_2 and IN NaOH. The organic phase was washed with IN HCl, then H_2O and dried over $MgSO_4$ and evaporated under reduced pressure. Purification on silica gel eluting with CH_2Cl_2/MeOH/0.88 NH_3 (98/1.25/0.25, v/v) initially and then (96/3.5.0.5, v/v) gave the subtitle compound as a gum (53%). R_f 0.44 (CH_2Cl_2/MeOH/0.88 NH_3 96/3.5/0.5, v/v). MS m/z 350 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.4 (9H, s), 1.9 (2H, m), 3.17 (4H, m), 3.22 (2H, m), 3.4 (2H, m), 3.5 (2H, m). 3.73 (6H, m).

(b) 1-(4-Morpholinesulphonyl)-1,4-diazepane hydrochloride.

[0055] The title compound was prepared by the method of Intermediate 1(c) from the product of step (a) above. The subtitle compound (97%) was obtained as a white solid. R_f 0.09 (CH_2Cl_2/MeOH/0.88 NH_3 92/7/1, v/v). MS m/z 250 (MH^+). ^1H NMR (d_6-DMSO) δ: 2.1 (2H ,m), 3.1 (4H, m), 3.4 (4H, m), 3.62 (8H, m), 9.2 (2H, b).

Intermediate 4

2-Acetyl-5-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline

(a) 5-Methanesulfonamidoisoquinoline

[0056] Methanesulfonyl chloride (3.2ml, 42mmol) was added to a solution of 5-aminoisoquinoline (5.0g, 35mmol) in pyridine (40ml) and the mixture was allowed to stand for 72h. The reaction mixture was then poured into aqueous citric acid (10%, 400ml) and extracted with EtOAc (2x230ml). The organic layer was evaporated to give a residue that was purified on silica gel, eluting with CH_2Cl_2/MeOH, to afford the subtitle compound as a solid (3.55g, 46%). R_f 0.03 (CH_2Cl_2/ether 4/1, v/v). ^1H NMR (D_6-DMSO) δ: 3.07 (3H, s), 7.68 (1H, t), 7.75 (1H, d), 8.03 (1H, d), 8.10 (1H, d), 8.54 (1H, d), 9.32 (1H, s). 9.79 (1H, bs).

(b) 5-Methanesulfonamido-1,2,3,4-tetrahydroisoquinoline hydrochloride

[0057] A solution of the product of step (a) (3.50g, 15.7mmol) in EtOH (250ml) was treated with platinum dioxide (1.5g) and 1N HCl (15.7ml). The mixture was hydrogenated at a pressure of 414 kPa (60 psi) for 16h, after which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure and triturated with CH_2Cl_2 to afford the subtitle compound as a colourless solid. The solid residue from the filtration was taken up into MeOH/H_2O (1:2, v/v), and the suspension filtered, washing with CH_2Cl_2 (3x). This filtrate was evaporated to afford a second crop of the subtitle compound (total yield 3.45g, 84%). R_f 0.21 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). ^1H NMR (D_6-DMSO) δ: 2.96-3.10 (2H, m), 3.31 (3H, m), 4.21 (2H, s), 7.12 (1H, m), 7.26 (2H, m), 9.24 (1H, s), 9.61 (2H, bs).

(c) 2-Acetyl-5-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline

[0058] To a solution of the product of step (b) (2.87g, 10.9mmol) in CH_2Cl_2 at 0°C was added acetic anhydride (1.2ml, 13.1mmol) and triethylamine (3.4ml, 24.0mmol), and the reaction was stirred at room temperature for 16h. The reaction mixture was then partitioned between EtOAc and aqueous sodium bicarbonate solution and the aqueous phase extracted with further portions of EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated to afford an oil. This was dissolved in MeOH (15ml) and treated with aqueous sodium carbonate solution (7%, w/w, 15ml) and the mixture stirred for 16h at room temperature, after which time the MeOH was removed under reduced pressure, the pH was adjusted to pH 8 with 2N HCl and the product was extracted with EtOAc (2x). The combined organic extracts were dried over $MgSO_4$ and evaporated to give an oil that was purified on silica gel, eluting with CH_2Cl_2/MeOH (95/5, v/v) to give the title compound as an oil (2.0g, 68%). R_f 0.20 (CH_2Cl_2/MeOH 9/5, v/v). MS m/z 269 (MH^+).

Example 1

4-Amino-7-methoxy-2-[4-(4-morpholinesulphonyl)-1,4-diazepan-1-yl]-6-phenyl-quinazoline hydrochloride

(a) 5-Hydroxy-4-methoxy-2-nitrobenzoic acid, methyl ester

[0059] To a solution of 5-hydroxy-4-methoxy-2-nitrobenzoic acid [Sinha J. Ind. Chem. Soc., 47, 925 (1970)] (83.0g, 0.39mol) in MeOH (250ml) was added concentrated H_2SO_4 (20ml) and the reaction mixture was heated to reflux for 16h. On cooling, the reaction mixture was poured into aqueous potassium carbonate solution and acetic acid was added until pH 4 was reached. The mixture was extracted with chloroform, the organic layer washed twice with H_2O and dried over $MgSO_4$. Evaporation under reduced pressure afforded the subtitle compound as yellow crystals (77.0g, 87%). R_f 0.30 (benzene/acetone 4/1, v/v); m.p. 146-9°C

(b) 4-Methoxy-2-nitro-5-trifluoromethanesulfonatobenzoic acid, methyl ester

[0060] To a solution of the product of step (a) (30.0g, 0.13mol) in CH_2Cl_2 (1.31) was added pyridine (32.0ml, 0.40mol) and the mixture stirred at room temperature for 66h, after which time it was cooled to -20°C and triflic anhydride (32.5ml, 0.20mol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 3h and then stirred for a further 3h. After this, H_2O (500ml) was added, the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to afford a yellow oil. This was passed through a pad of silica gel, washing with CH_2Cl_2, and evaporated to afford a yellow solid which on recrystallisation with Et_2O afforded the subtitle compound as a colourless solid (39.6g, 85%). R_f 0.50 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 377 (MNH_4^+)

(c) 4-Methoxy-2-nitro-5-phenylbenzoic acid, methyl ester

[0061] A solution of the product of step (b) (15.0g, 40mmol) in toluene (200ml) and EtOH (100ml) was treated with phenylboronic acid (6.1g, 50mmol), tetrakis(triphenylphosphine)palladium (2.4g, 2mmol) and 2N aqueous sodium carbonate (45ml) and the mixture was heated to reflux for 1h. The mixture was then cooled and partitioned between EtOAc and H_2O. The organic layer was separated, dried over $MgSO_4$, evaporated under reduced pressure and then passed through a plug of silica gel, washing with CH_2Cl_2, evaporated under reduced pressure and the solid purified by trituration with hexane. This afforded the subtitle compound as an off-white solid (11.4g, 99%). R_f 0.48 (CH_2Cl_2). MS m/z 305 (MNH_4^+).

(d) 2-Amino-4-methoxy-5-phenylbenzoic acid, methyl ester

[0062] To a solution of the product of step (c) (12.19g, 43mmol) in CH_2Cl_2 (200ml) was added tetra-n-butylammonium chloride (7.1g, 26mmol) followed by a suspension of sodium dithionite monohydrate (81.6g, 430mmol) in H_2O (250ml) and the resulting mixture was stirred rapidly for 30min at room temperature. A further portion of sodium dithionite monohydrate (40.8g, 215mmol) in H_2O (150ml) was added and stirring continued for a further 30min at room temperature. The mixture was then basified with 2N aqueous NaOH, the organic layer separated, dried over $MgSO_4$ and concentrated to 100ml under reduced pressure. Treatment with excess ethereal HCl was followed by neutralisation with 2N aqueous NaOH and the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to give a green oil. Purification on silica gel, eluting with EtOAc afforded the subtitle compound as a yellow oil (10.76g, 99%). R_f 0.79 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 258 (MH^+).

(e) 7-Methoxy-6-phenylquinazoline-2,4-dione

[0063] To a solution of the product of step (d) (10.75g, 41.8mmol) in CH_2Cl_2 (200ml) was added sodium cyanate (10.88g, 167mmol) followed by trifluoroacetic acid (13.3ml, 167mmol) and the reaction was stirred for 18h at room temperature. The mixture was then partitioned between CH_2Cl_2 and H_2O, the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to afford a yellow solid. This was suspended in aqueous NaOH (16.7g in 150ml H_2O) and warmed to 70°C for 1h after which time the mixture was cooled, acidified with concentrated HCl, and the resulting solid filtered and washed sequentially with water and acetone. This afforded the subtitle compound as an off-white solid (10.16g, 91%). R_f 0.16 (CH_2Cl_2/MeOH 95/5, v/v). ^1H NMR (D_6-DMSO) δ: 3.85 (3H, s), 7.35 (2H, m), 7.45 (3H, m), 7.70 (1H, s), 7.75 (1H, s), 11.10 (2H, bd).

(f) 4-Amino-2-chloro-7-methoxy-6-phenylquinazoline

[0064] The product of step (e) (10.15g, 40mmol) was combined with phosphorus oxychloride (52.8ml, 570mmol) and *N,N*-dimethylaniline (12.0ml, 90mmol) and the mixture was heated to reflux for 1.5h. The reaction mixture was then evaporated under reduced pressure, azeotroping with toluene (2x), and the resulting solid was partitioned between EtOAc and H_2O. The organic layer was separated and dried over $MgSO_4$, then passed through a plug of silica gel, washing with EtOAc, and evaporated to afford a yellow solid. This was dissolved in CH_2Cl_2 and treated with saturated methanolic NH_3 (150ml) and the reaction stirred for 48h at room temperature. Evaporation followed by suspension in MeOH and filtration, washing with ether, afforded the subtitle compound as a white solid (5.94g, 55%). R_f 0.57 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 286 (MH^+).

(g) 4-Amino-7-methoxy-2-[4-(4-morpholinesulphonyl)-1,4-diazepan-1-yl]-6-phenylquinazoline hydrochloride

[0065] To a solution of the product of step (f) (300mg, 1.05mmol) and Intermediate 3 (300mg, 1.05mmol) in n-BuOH (5ml) was added triethylamine (0.31ml, 2.2mmol), and the mixture was heated at 100°C for 18h. After cooling, the reaction mixture was evaporated under reduced pressure, partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$ to afford a brown solid. Trituration in hot isopropanol afforded the title compound as a colourless solid (86mg, 16%). R_f 0.22 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 499 (MH^+). 'H NMR (D_6-DMSO) δ: 1.90 (2H, m), 3.00 (4H, m), 3.45 (2H, m), 3.60 (6H, m), 3.90 (3H, s), 3.94 (2H, m), 4.00 (2H, m), 7.35-7.55 (5H, m), 7.65 (1H, bs), 8.20 (1H, s), 8.73 (1H, bs), 8.89 (1H, bs), 12.10 (1H, bs). Found: C,52.42; H,5.96; N,14.39. $C_{24}H_{31}N_6O_4SCl\ H_2O$ 0.3.isopropanol 0.5.EtOAc 0.5.H_2O requires C,52.37; H,6.25; N,14.72%.

Example 2

4-Amino-7-methoxy-6-phenyl-2-[4-(thiomorpholine-1,1-dioxide-4-carbonyl)-1,4-diazepan-1-yl]quinazoline hydrochloride

(a) Thiomorpholine-1,1-dioxide hydrochloride

[0066] 2-Chloroethyl chloroformate (0.72ml, 6.7mmol) was added dropwise to a solution of 4-methylthiomorpholine-1,1-dioxide (1.0g, 6.7mmol) in toluene (10ml) at 0°C under N_2. After 10min, the reaction was warmed and maintained at reflux for 2h. On cooling, the reaction mixture was evaporated and partitioned between EtOAc and H_2O. The organic layer was separated and washed sequentially with dilute HCl and saturated brine, then dried over Na_2SO_4 and evaporated. The residue was taken up in MeOH (10ml) and heated at reflux for 2h, after which time the mixture was evaporated and triturated with EtOAc to afford the subtitle compound (415mg, 36%) as a solid. R_f 0.34 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 136 (MH^+).

(b) Thiomorpholine-1,1-dioxide-4-carbonyl chloride

[0067] A solution of the product of step (a) (170mg, 1.0mmol) in CH_2Cl_2 (20ml) at -20°C was treated sequentially with *N,N*-diisopropylethylamine (0.23ml, 1.32mmol) and triphosgene (90mg, 0.31mmol) and the reaction mixture stirred under N_2 for 1h at room temperature. Evaporation under reduced pressure afforded the crude subtitle compound (207mg, quantitative) which was used without further purification. R_f 0.76 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v).

(c) 4-Amino-7-methoxy-6-phenyl-2-[4-(thiomorpholine-1,1-dioxide-4-carbonyl)-1,4-diazepan-1-yl]quinazoline hydrochloride

[0068] To a solution of the compound of Example 1(f) (300mg, 1.05mmol) in n-BuOH (20ml) was added homopiperazine (1.05g, 10.5mmol) and the mixture was heated to 100°C for 5h. After this, the reaction mixture was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 and 2N aqueous NaOH. The organic layer was separated, dried over $MgSO_4$ and evaporated to afford a foam. This was taken up in THF (20ml), triethylamine (0.15ml, 1.1mmol) was added, followed by the product of step (b) (207mg, 1.0mmol), and the mixture was heated at reflux for 3h. After cooling, the reaction mixture was evaporated under reduced pressure and partitioned between CH_2Cl_2 and 2N aqueous NaOH. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (97/3, v/v) and then converted to the hydrochloride salt by treatment with excess ethereal HCl. This afforded the title compound as a colourless solid (130mg, 23%). R_f 0.76 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 511 (MH^+). 'H NMR (D_6-DMSO) δ: 1.94 (2H, m), 3.06 (4H, m), 3.34 (6H, m), 3.65 (2H, m), 3.86 (5H, m), 4.01 (2H, bm), 7.30-7.55 (5H, m), 7.80 (1H, bm), 8.19 (1H,

s), 8.70 (1H, bs), 8.87 (1H, bs), 12.15 (1H, bs). Found: C,51.63; H,5.99; N,14.25. $C_{25}H_{31}N_6O_4SCl\ 2.H_2O$ requires C, 51.50; H,6.05; N,14.41%.

Example 3

4-Amino-2-[4-(1,4-benzodioxan-2-carbonyl)-1,4-piperazin-1-yl]-7-methoxy-6-phenylquinazoline

[0069] Prepared by a method analogous to Example 1(g) from the compound of Example 1(f) and 1-(1,4-benzodioxan-2-ylcarbonyl)piperazine [Campbell *et al.* J. Med. Chem., 30, 49 (1987)]. MS m/z 498 (MH^-)

Example 4

(R/S)-4-Amino-7-methoxy-6-phenyl-2-[4-(tetrahydrofuran-2-carbonylamino)-1-propaneamino]quinazoline

(a) 4-Amino-7-methoxy-6-phenyl-2-[*N*-(1,3-diaminopropyl)]quinazoline

[0070] To a solution of the compound of Example 1(f) (1.0g, 3.50mmol) in n-BuOH (15ml) was added 1,3-diaminopropane (2.9ml, 35.0mmol) and potassium iodide (5mg) and the reaction mixture was heated to 100°C for 18h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue suspended in CH_2Cl_2 and isolated by filtration. The solid was partitioned between EtOAc and 2N NaOH, the organic layer dried over $MgSO_4$ and evaporated under reduced pressure to afford the subtitle compound as a colourless foam (613mg, 54%). R_f 0.07 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 324 (MH^+).

(b) (R/S)-4-Amino-7-methoxy-6-phenyl-2-[4-(tetrahydrofuran-2-carbonylamino)-1-propaneamino]quinazoline

[0071] To a solution of the product of step (a) (250mg, 0.77mmol) in CH_2Cl_2 was added (R/S)-tetrahydrofuran-2-carboxylic acid (99mg, 0.85mg), 1 -hydroxybenzotriazole hydrate (157mg, 1.16mmol), 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (223mg, 1.16mmol) and triethylamine (0.16ml, 1.16mmol) and the reaction was stirred at room temperature under N_2 for 18h. The reaction mixture was partitioned between CH_2Cl_2 and 2N NaOH, the organic layer was separated. dried over $MgSO_4$, and evaporated under reduced pressure to afford a colourless solid. This was recrystallised in EtOAc to afford the title compound as a colourless solid (143mg, 44%). R_t 0.58 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 422 (MH^+). ^1H NMR (D_6-DMSO) δ: 1.62 (2H, m), 1.82 (2H, m), 1.90 (1H, m), 2.05 (1H, m), 3.04 (1H, m), 3.20-3.45 (5H, m), 3.75-3.84 (1H, m), 3.80 (3H, s), 4.23 (1H, m), 6.50 (1H, bs), 6.88 (1H. s), 7.20 (1H, bs), 7.30 (1H, m), 7.40 (2H, m), 7.50 (2H, m), 7.93 (1H, s). 8.04 (1H, bs). Found: C,64.11; H,6.50; N,15.87, $C_{23}H_{27}N_5O_3$ 0.6.H_2O requires C,63.90; H,6.58; N,16.20%.

Example 5

(R/S)-4-Amino-7-methoxy-6-phenyl-2-[4-(tetrahydrofuran-2-carbonylamino)-1-*N*-methylpropaneamino] quinazoline

[0072] The title compound was prepared from the compound of Example 1(f) by the method of Example 4, but using N-methyl-1,3-propanediamine in place of 1,3-diaminopropane. MS m/z 436 (MH^+).

Example 6

4-Amino-7-methoxy-6-phenyl-2-[4-(4-morpholinecarbonyl-*N*-methylamino)propaneamino]quinazoline

[0073] The title compound was prepared by the method of Example 4(a) from the compound of Example 1(f) and N-methyl-1,3-propanediamine, followed by reaction with 4-morpholinecarbonyl chloride using the method of Intermediate 1(b). MS m/z 498 (MH^+).

Example 7

4-Amino-7-methoxy-6-phenyl-2-[4-(tetrahydrofuran-2-carbonyl)-1,4-piperazin-1-yl]-quinazoline

[0074] The title compound was prepared by the method of Example 4 from the compound of Example 1(f), but using piperazine in place of 1,3-diaminopropane. MS m/z 434 (MH^+).

Example 8

4-Amino-7-methoxy-2-[4-(morpholinecarbonylamino)-1-propaneamino]-6-phenylquinazoline

[0075] The compound of Example 4(a) was reacted with 4-morpholinecarbonyl chloride using the method of Intermediate 1(b) to give the title compound. MS m/z 437 (MH^+).

Example 9

4-Amino-7-methoxy-2-[4-(morpholinecarbonylamino)-1-*N*-methylpropaneamino]-6-phenylquinazoline

[0076] The title compound was prepared from the compound of Example 1(f) by the method of Example 4(a), but using N-methyl-1,3-propanediamine in place of 1,3-diaminopropane, followed by reaction with 4-morpholinecarbonyl chloride using the method of Intermediate 1(b). MS m/z 451 (MH^+)

Example 10

4-Amino-7-methoxy-6-phenyl-2-(5,6,7,8-tetrahydro-1,6-naphthyrid-6-yl)guinazoline

[0077] The title compound was prepared by the method of Example 1(g) from the compound of Example 1(f) and 5,6,7,8-tetrahydro-1,6-naphthyridine [Shiozawa *et al.* Chem. Pharm. Bull., 32, 2522 (1984)]. MS m/z 384 (MH^+).

Example 11

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-phenylquinazoline

(a) 3-Benzyloxy-4-methoxybenzonitrile

[0078] 3-Benzyloxy-4-methoxybenzaldehyde (50g, 0.21mol) was added to a solution of sodium acetate (33.9g, 0.41mol) and hydroxylamine hydrochloride (28.73g, 0.41mol) in acetic acid (200ml) and the resulting suspension was heated to reflux for 18h. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and H_2O and the aqueous phase was further extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the subtitle compound as a buff-coloured solid (43.9g, 89%). R_f 0.70 (toluene/EtOAc 4/1, v/v).

(b) 5-Benzyloxy-4-methoxy-2-nitro-benzonitrile

[0079] A solution of the product of step (a) (43.8g, 0.18mol) in glacial acetic acid (87ml) was added dropwise to concentrated nitric acid (70% w/w, 244ml) with periodic cooling to maintain the reaction temperature below 30°C. Once the addition was complete, the reaction was stirred for a further 30min, after which time the mixture was poured into H_2O (11) and stirred for 30min. The resulting precipitate was isolated by filtration, washed with H_2O and dried under reduced pressure at 50°C to afford the subtitle compound as a white solid (35.1g, 68%). R_f 0.70 (EtOAc/hexane 1/1, v/v).

(c) 2-Amino-5-benzyloxy-4-methoxybenzonitrile

[0080] To a solution of the product of step (b) (35.0g, 0.12mol) in CH_2Cl_2 (500ml) was added tetra-n-butylammonium chloride (20.3g, 0.074mol) followed by a solution of sodium dithionite hydrate (118.0g, 0.61mol) in H_2O (400ml) and the mixture was stirred vigorously for 2h at room temperature. A further quantity of sodium dithionite hydrate (47.2g) was then added and stirring continued for 1h. The reaction mixture was then basified with 2N aqueous NaOH and the phases separated. The aqueous layer was extracted twice more with CH_2Cl_2 and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure to a volume of 60ml. Treatment with excess ethereal HCl led to the precipitation of an orange solid that was washed with ether and then dissolved in a mixture of CH_2Cl_2 and 2N aqueous NaOH. The phases were separated and the organic layer concentrated under reduced pressure and then dissolved in EtOAc and passed through a 5cm plug of silica gel, eluting with EtOAc. On evaporation and drying under reduced pressure, the subtitle compound was obtained as a yellow solid (26.7g, 85%). R_f 0.76 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 255 (MH^+).

(d) 4-Amino-6-benzyloxy-2-hydroxy-7-methoxyquinazoline

[0081] A solution of the product of step (c) (26.7g, 0.10mol) in CH_2Cl_2 was treated with sodium cyanate (17.1g, 0.26mol) and trifluoroacetic acid (20.9ml, 0.26mol) was added dropwise to the resulting mixture at room temperature. After 45min, the mixture was diluted with CH_2Cl_2 (11) and stirred for a further 18h. The mixture was then concentrated under reduced pressure and partitioned between MeOH and 2N aqueous NaOH and stirred for 2h. The MeOH was then removed under reduced pressure and the yellow solid isolated by filtration, washing sequentially with H_2O, acetone and ether to afford the subtitle compound as a yellow solid (18.0g, 54%). A further quantity of product was obtained by concentration of the filtrate, acidification with concentrated HCl (95ml), warming on a steam bath for 5min, cooling and neutralisation with solid potassium carbonate. The solid obtained was isolated by filtration, washing sequentially with H_2O, EtOH and ether to afford the subtitle compound as a yellow solid (12.11g, 93% combined yield). R_f 0.23 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 298 (MH^+).

(e) 4-Amino-6-benzyloxy-2-chloro-7-methoxyquinazoline

[0082] DMF (7.9ml, 0.10mol) was added dropwise to phosphorus oxychloride (47.9ml, 0.52mol) with stirring. After 10min, the product of step (d) (16.4g, 0.055mol)was added portionwise and the resulting mixture heated at 90°C for 1.5h, then cooled and poured into EtOAc (750ml). The mixture was neutralised by the portionwise addition of aqueous sodium carbonate and the phases were separated. The organic layer was evaporated to dryness and the residue combined with the organic phase that was then treated with aqueous NaOH to basify (pH10) and the mixture was heated at 90°C for 2h. After cooling, the mixture was partitioned between CH_2Cl_2 (11) and H_2O (11), the organic phase washed with H_2O, dried over $MgSO_4$ and evaporated to give a pale yellow solid. Trituration with isopropanol afforded the subtitle compound as a colourless solid (4.64g, 27%). R_f 0.64 (EtOAc/MeOH 95/5, v/v). MS m/z 316, 318 (MH^+).

(f) 4-Amino-6-benzyloxy-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

[0083] The subtitle compound was prepared by the method of Example 1(g) from the product of step (e) and Intermediate 1. The product was purified on silica gel eluting with EtOAc/MeOH (9/1, v/v) to afford the subtitle compound (46%) as a foam. R_f 0.67 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 493 (MH^+).

(g) 4-Amino-6-hydroxy-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

[0084] The product of step (f) (360mg, 0.73mmol) was dissolved in EtOH (60ml), 10% palladium on charcoal (100mg, 0.09mmol) was added and the reaction mixture hydrogenated at room temperature at a pressure of 414 kPa (60 psi) for 18h. The reaction mixture was filtered and concentrated under reduced pressure and the residue purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (92/7/1, v/v) to afford the subtitle compound as foam (135mg, 47%). R_f 0.33 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 403 (MH^+).

(h) 4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-trifluoromethylsulfonatoquinazoline

[0085] To a solution of the product of step (g) (3.3g, 8.2mmol) in CH_2Cl_2 (80ml), pyridine (2.0ml, 25mmol) was added. The solution was cooled to -20°C and triflic anhydride (2.0ml, 12.3mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for a further 18h, after which time it was partitioned between CH_2Cl_2 and H_2O, the solid residue dissolved in EtOAc and the organic layers combined, washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (96/3.5/0.5, v/v) to afford the subtitle compound as a colourless solid (2.5g, 57%). R_f 0.36 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 535 (MH^+).

(i) 4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-phenylquinazoline

[0086] To a solution of the product of step (h) (200mg, 0.37mmol) in dioxan (5ml) was added trimethylphenylstannane (0.71ml, 0.37mmol), lithium chloride (48mg, 1.11mmol) and tetrakis(triphenylphosphine)palladium (9mg, 0.007mmol) and the reaction mixture heated to reflux for 18h under N_2. After cooling and evaporation under reduced pressure, the residue was dissolved in CH_2Cl_2, filtered through a pad of Hyflo® diatomaceous earth and evaporated under reduced pressure. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (95/5, v/v) to afford the title compound as a colourless foam (65mg, 38%). R_f 0.28 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 463 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.04 (2H, m), 3.14 (4H, m), 3.34 (2H, m), 3.54 (2H, m), 3.66 (4H, m), 3.86 (5H, m), 4.00 (2H, m), 5.17 (2H, bs), 6.90 (1H, s), 7.18-7.46 (4H, m), 7.53 (2H, m). Found: C,61.90; H,6.34; N,17.29. $C_{25}H_{30}N_6O_3$ 0.1H_2O 0.3CH_2Cl_2

requires C,62.04; H,6.34; N,17.16%

Example 12

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-(2-pyridinyl)-quinazoline

[0087] The title compound was prepared by the method of Example 11(i) from the compound of Example 11(h), but using (2-pyridinyl)tributylstannane in place of trimethylphenylstannane. MS m/z 464 (MH^+).

Example 13

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-(3-pyridinyl)-quinazoline

[0088] To a suspension of the compound of Example 11(h) (300mg, 0.56mmol) in a mixture of H_2O (1ml) and THF (6ml) was added 3-pyridinyldiethylborane (82mg, 0.56mmol), tetrakis(triphenylphosphine)palladium (32mg, 0.028mmol), tetra-n-butylammonium chloride (15mg, 0.056mmol) and KOH (94mg, 1.68mmol) and the reaction mixture was heated to reflux for 3h. After cooling, the reaction mixture was partitioned between EtOAc and H_2O, the organic layer separated, dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v) followed by recrystallisation from CH_2Cl_2/hexane to afford the title compound as a white solid (42mg, 16%). R_f 0.16 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 464 (MH^+), ^1H NMR ($CDCl_3$) δ: 2.05 (2H, m), 3.18 (4H, m), 3.35 (2H, m), 3.56 (2H, m), 3.66 (4H, m), 3.90 (5H, m), 4.03 (2H, m), 5.30 (2H, bs), 6.93 (1H, s), 7.32 (1H, m), 7.43 (1H, s), 7.86 (1H, m), 8.55 (1H, d), 8.73 (1H, s). Found: C, 60.14; H,6.17; N,20.14. $C_{24}H_{29}N_7O_3$ 0.9.H_2O requires C,60.09; H,6.47; N,20.44%

Example 14

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-(4-pyridinyl)-quinazoline

[0089] To a solution of the compound of Example 11(h) (290mg, 0.54mmol) in a mixture of EtOH (6ml) and toluene (10ml) was added 4-pyridineboronic acid [Fischer *et al* Recl. Trav. Chim. Pays Bas, 93, 21 (1974)] (100mg, 0.81mmol) tetrakis(triphenylphosphine)palladium (31mg, 0.027mmol) and 2N aqueous Na_2CO_3 (2ml) and the mixture was heated to reflux for 3h. After cooling, the reaction mixture was partitioned between EtOAc and H_2O, the organic layer dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v) then triturated sequentially with EtOAc and CH_2Cl_2 to afford the title compound as a colourless solid (80mg, 32%). R_f 0.20 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 464 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.02 (2H, m), 3.16 (4H, m), 3.35 (2H, m), 3.54 (2H, m), 3.64 (4H, m), 3.88 (5H, m), 4.00 (2H, m), 5.27 (2H, bs), 6.90 (1H, s), 7.45 (3H, m), 8.65 (2H, m). Found: C,60.78; H,6.22; N,20.24. $C_{24}H_{29}N_7O_3$ 0.7.H_2O requires C,60.54; H,6.44; N,20.59%

Example 15

4-Amino-6-(2-furyl)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-quinazoline

[0090] The title compound was prepared by the method of Example 14 from the compound of Example 11(h), but using 2-furanylboronic acid [Florentin *et al.* J. Heterocyclic Chem., 13, 1265 (1976)] in place of 4-pyridineboronic acid. MS m/z 453 (MH^+)

Example 16

4-Amino-6-(3-furyl)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-quinazoline

[0091] The title compound was prepared by the method of Example 14 from the compound of Example 11(h), but using 3-furanylboronic acid [Florentin *et al.* J. Heterocyclic Chem., 13, 1265 (1976)] in place of 4-pyridineboronic acid. MS m/z 453 (MH^+).

Example 17

4-Amino-6-(4-aminosulfonylphenyl)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

(a) (4-Aminosulphonylphenyl)tributylstannane

[0092] To a solution of p-bromobenzenesulfonamide [Huntress *et al.* J. Am. Chem. Soc., 62, 511 (1940)] (1.5g, 6.4mmol) in toluene (10ml) was added hexabutylditin (7.3ml, 19.2mmol) and tetrakis(triphenylphosphine)palladium (73mg, 0.063mmol) and the reaction mixture was heated to 80°C for 3h, after which time it was cooled and the resulting suspension passed through a plug of silica gel, washing sequentially with toluene and EtOAc. The EtOAc washings were evaporated under reduced pressure and the residue purified by chromatography on silica gel, eluting with EtOAc/hexane (1/4, v/v) to give the subtitle compound as an oil (1.0g, 36%). R_f 0.47 (EtOAc/hexane 1/1, v/v).

(b) 4-Amino-6-(4-aminosulfonylphenyl)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

[0093] The title compound was prepared by the method of Example 11(i) from the compound of Example 11(h), but using the compound of step (a) in place of trimethylphenylstannane. MS m/z 542 (MH^+).

Example 18

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-phenylquinoline

(a) 5-(Benzyloxy)-4-methoxy-2-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-ethylideneamino}benzonitrile

[0094] To a solution of Intermediate 2 (6.02g, 23.6mmol) in CH_2Cl_2 (100ml) was added dropwise phosphorus oxychloride (1.31ml, 12.9mmol). The mixture was stirred for 20min at room temperature and then the compound of Example 11(c) (3.0g, 11.7mmol) was added and the suspension was heated at reflux for 18h. After cooling, the reaction mixture was partitioned between CH_2Cl_2 (150ml) and aqueous 1N NaOH (100ml), the organic phase separated, dried over $MgSO_4$ and evaporated to afford a yellow foam. The product was purified by chromatography on silica gel, eluting with EtOAc/MeOH (97/3, v/v) to afford the subtitle compound as a pale yellow glass (3.35g, 58%). R_f 0.54 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 492 (MH^+).

(b) 5-Hydroxy-4-methoxy-2-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-ethylideneamino}benzonitrile

[0095] The subtitle compound was prepared by the method of Example 11(g) from the product of step (a). This afforded the subtitle compound (90%) as a colourless solid. R_f 0.47 (CH_2Cl_2/MeOH 9/1, v/v).

(c) 4-Methoxy-2-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]ethylideneamino}-5-(trifluoromethanesulfonato) benzonitrile

[0096] The subtitle compound was prepared by the method of Example 11(h) from the product of step (b). This afforded the subtitle compound (54%). R_f 0.70 (CH_2Cl_2/MeOH 9/1, v/v)

(d) 4-Methoxy-2-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]ethylideneamino}-5-phenylbenzonitrile

[0097] The subtitle compound was prepared by the method of Example 14 from the product of step (c) using phenylboronic acid. This afforded the subtitle compound as a colourless solid (75%). R_f 0.34 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 461 (MH^+).

(e) 4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-phenylquinoline

[0098] To a solution of the product of step (e) (315mg, 0.68mmol) in THF (10ml) at -20°C was added a solution of lithium diisopropylamide in THF (0.68M, 2ml, 1.36mmol) and the reaction allowed to warm to room temperature. The reaction mixture was poured into cooled 1N citric acid, the solution basified with Na_2CO_3 and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to afford a residue that was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (90/10/1, v/v) followed by trituration with EtOAc to afford the title compound as an off-white solid (109mg, 35%). R_f 0.46 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 462 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.08 (2H, m), 3.12 (4H, m), 3.37 (2H, m), 3.64 (6H, m), 3.75 (2H, m), 3.90 (3H, s), 4.02 (2H, m), 4.41 (2H, bs), 5.96

(1H, s), 7.07 (1H, bs), 7.37 (1H, m), 7.46 (3H, m), 7.58 (2H, m). Found: C,65.28; H,6.89; N,14.15. $C_{26}H_{31}N_5O_3$ H_2O 0.1.EtOAc requires C,64.93; H,6.98; N,14.34%

Example 19

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-(2-pyridinyl)-quinoline

(a) 4-Methoxy-2-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]ethylideneamino}-5-(2-pyridinyl)benzonitrile

[0099] The subtitle compound was prepared by the method of Example 11(i) from the compound of Example 18(c) and (2-pyridinyl)tri-n-butylstannane.

(b) 4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-(2-pyridinyl)quinoline

[0100] The title compound was prepared by the method of Example 18(e) from the compound of step (a). MS m/z 463 (MH^+).

Example 20

4-Amino-7-methoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-6-(2-pyridinyl)quinoline

(a) 4-Methoxy-2-nitro-5-(2-pyridinyl)benzoic acid, methyl ester

[0101] The subtitle compound was prepared from the compound of Example 1(b) by the method of Example 11(i) using (2-pyridinyl)tri-n-butylstannane. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (99:1) followed by trituration with ether to afford the subtitle compound (39%) as a colourless solid. R_f 0.64 (CH_2Cl_2/MeOH/ 95/5, v/v). MS m/z 289 (MH^+).

(b) 4-Methoxy-2-nitro-5-(2-pyridinyl)benzamide

[0102] To a suspension of the product of step (a) (3.30g, 11.5mmol) in MeOH (100ml) was added 2N aqueous NaOH (6.3ml, 12.6mmol) and the reaction mixture was stirred for 64h at room temperature followed by heating to reflux for 6h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue suspended in CH_2Cl_2 (100ml) and DMF (0.5ml) was added. Oxalyl chloride (3.06ml, 34.4mmol) was then added and the mixture was stirred rapidly at room temperature for 4h then evaporated under reduced pressure. The residue was suspended in CH_2Cl_2 and poured into a rapidly stirred solution of 0.88 aqueous NH_3. The resulting mixture was stirred for 15min and the solid formed was isolated by filtration, washing with CH_2Cl_2 and H_2O. The solid was dried under vacuum at 65°C for 18h to afford the subtitle compound as a colourless solid (2.50g, 80%). R_f 0.27 (EtOAc). MS m/z 274 (MH^+).

(c) 4-Methoxy-2-nitro-5-(2-pyridinyl)benzonitrile

[0103] A solution of the product of step (b) (2.40g, 8.8mmol) in CH_2Cl_2 was treated with trifluoroacetic anhydride (20ml) and the reaction mixture stirred for 2h at room temperature and at reflux for a further 1h. After cooling, the reaction mixture was evaporated under reduced pressure, the residue basified with 1N aqueous NaOH and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with EtOAc to afford the subtitle compound (1.73g, 77%). R_f 0.58 (EtOAc). MS m/z 256 (MH^+).

(d) 2-Amino-4-methoxy-5-(2-pyridinyl)benzonitrile

[0104] The subtitle compound was prepared by the method of Example 1(d) from the product of step (c). The product was purified by chromatography on silica gel, eluting with EtOAc to afford the subtitle compound (69%) as a yellow solid. R_f 0.46 (EtOAc). MS m/z 226 (MH^+).

(e) 2-[1-(5-Methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)ethylideneamino]-4-methoxy-5-(2-pyridinyl) benzonitrile

[0105] The subtitle compound was prepared by the method of Example 18(a) from the product of step (d) and Inter-

mediate 4. The product was purified by chromatography on silica gel. eluting with EtOAc, followed by trituration with ether to afford the subtitle compound (61%) as a pale yellow solid. R_f 0.35 (EtOAc). MS m/z 476 (MH^+).

(f) 4-Amino-7-methoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-6-(2-pyridinyl)quinoline

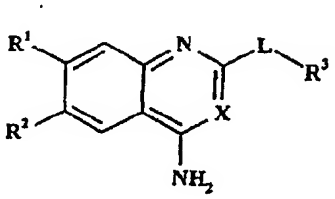
[0106] To a solution of the product of step (e) (961mg, 2.0mmol) in DMSO (12ml) was added KOH (226mg, 4.0mmol) and the mixture was heated to 95°C under N_2 for 20min. After cooling, the reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The organic layer was washed sequentially with H_2O and saturated brine then dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (92/7/1, v/v) followed by trituration with ether to afford the title compound as a colourless solid (656mg, 69%). R_f 0.14 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 476 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 2.82 (2H, m), 2.99 (3H, s), 3.88 (2H, m), 3.93 (3H, s), 4.64 (2H, bs), 4.82 (2H, s), 6.58 (1H, bs), 7.05-7.15 (6H, m), 7.67 (1H, t), 7.88 (1H, d), 8.07 (1H, s). 8.63 (1H, d). Found: C,59.84; H,5.38; N,13.51. $C_{25}H_{25}N_5O_3S$ 1.5. H_2O requires C,59.75; H,5.62; N,13.93%

Example 21

[0107] The compound of Example 11 was tested in the first screen described above ("*Contractile responses of human prostate*") and found to have a pA_2 value of 8.7.

Claims

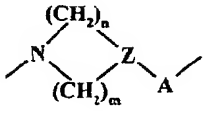
1. A compound of formula I,



I

wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;
R^2 represents phenyl, naphthyl, or an aromatic heterocycle having 5 or 6 ring members, at least one of which is N, O or S, optionally substituted by C_{1-4} alkyl or SO_2NH_2;
R^3 represents a 4-, 5-, 6-, or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by one or two oxygen atoms;
X represents CH or N; and
L is absent,
or represents a cyclic group of formula Ia,

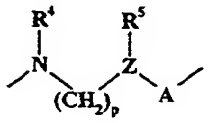


Ia

in which A is attached to R^3;
A represents CO or SO_2;
Z represents CH or N;
m represents 1 or 2, and in addition, when Z represents CH, it may represent 0; and

n represents 1, 2 or 3, provided that the sum of m and n is 2, 3, 4 or 5;

or represents a chain of formula Ib,



Ib

in which A is attached to R^3;
A and Z are as defined above;
R^4 and R^5 independently represent H or C_{1-4} alkyl; and
p represents 1, 2 or 3, and in addition, when Z represents CH, it may represent 0;

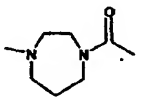
or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R^1 represents methoxy.

3. A compound as claimed in claim 1 or claim 2, wherein R^2 represents phenyl or 2-pyridinyl.

4. A compound as claimed in any preceding claim, wherein R^3 represents morpholinyl, or a piperidine ring which is fused to a benzene or pyridine ring.

5. A compound as claimed in any preceding claim, wherein L is absent or represents



6. A compound as claimed in claim 5, wherein L is absent and R^3 represents a piperidine ring fused to a benzene ring which is substituted by $NHSO_2(C_{1-4}$ alkyl).

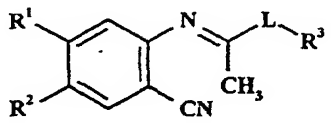
7. A pharmaceutical formulation including a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

9. The use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of benign prostatic hyperplasia,

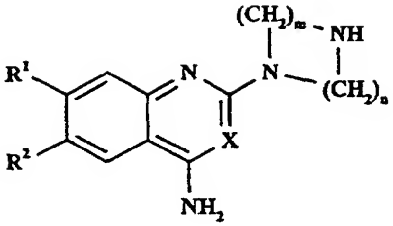
10. A process for the production of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises:

(a) when X represents CH, cyclizing a compound of formula II,

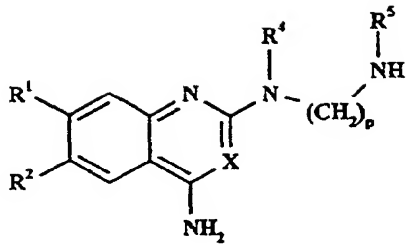


II

in which R^{1-3} and L are as defined in claim 1; or
(b) when Z represents N, reacting a compound of formula IIIa or IIIb, as appropriate,



IIIa

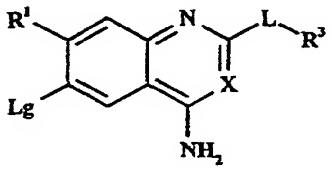


IIIb

in which R^1, R^2, R^4, R^5, X, m, n and p are as defined in claim 1, with a compound of formula IV,

$$Lg\text{-}A\text{-}R^3 \qquad IV$$

in which R^3 is as defined in claim 1, A represents CO or SO_2 and Lg represents a leaving group; or
(c) reacting a compound of formula V,

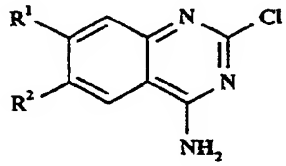


V

in which R^1, R^3, X and L are as defined in claim 1, and Lg is a leaving group, with a compound of formula VI,

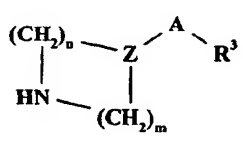
$$R^2\text{-}M \qquad VI$$

in which R^2 is as defined in claim 1 and M represents substituted boron, zinc or tin, in the presence of a palladium catalyst; or
(d) when X represents N, reacting a compound of formula VII,

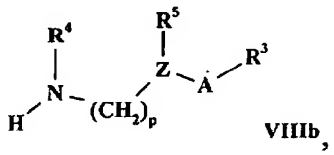


VII

in which R^1 and R^2 are as defined in claim 1, with a compound of formula VIIIa, VIIIb or VIIIc, as appropriate,



VIIIa,

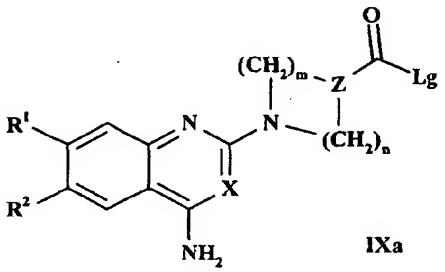


VIIIb,

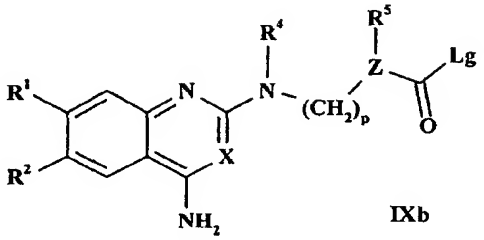
$$HR^{3a} \qquad VIIIc$$

in which R^{3-5}, A, Z, m, n and p are as defined in claim 1; and R^{3a} has the same significance as R^3 in claim 1 except that it contains a nucleophilic nitrogen atom in the heterocyclic ring which is attached to the H in formula

VIIIc; or
(e) when A represents CO and R^3 comprises a nucleophilic nitrogen atom in the heterocyclic ring attached to L, reacting a compound of formula IXa or IXb, as appropriate,



IXa



IXb

in which R^1, R^2, R^4, R^5, X, Z, m, n and p are as defined in claim 1, and Lg is a leaving group, with a compound of formula VIIIc, as defined above; or
(f) conversion of a compound of formula I in which L represents a cyclic group of formula Ia, to a corresponding compound of formula I in which L represents a chain of formula Ib in which R^4 and R^5 each represent H, by the action of a strong base; and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable salt or vice versa.

11. Compounds of formulae II, IIIa, IIIb and VII as defined in claim 10.

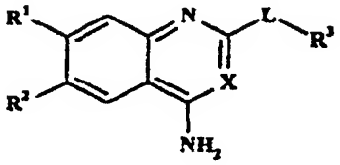
12. A compound of formula V, as defined in claim 10, wherein Lg represents the triflate group, $-OSO_2CF_3$.

13. A compound of formula IXa, as defined in claim 10, wherein Lg represents chloro.

14. A compound of formula IXb, as defined in claim 10, wherein Lg represents chloro.

Patentansprüche

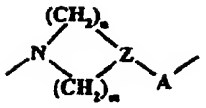
1. Verbindung der Formel I



I

worin

R^1 C_{1-4}-Alkoxy, gegebenenfalls substituiert mit einem oder mehreren Fluoratomen, wiedergibt;
R^2 Phenyl, Naphthyl oder einen aromatischen Heterocyclus mit 5 oder 6 Ringgliedern, wobei mindestens eines davon N, O oder S darstellt, gegebenenfalls mit C_{1-4}-Alkyl oder SO_2NH_2 substituiert, wiedergibt;
R^3 einen 4-, 5-, 6- oder 7-gliedrigen heterocyclischen Ring, enthaltend mindestens ein Heteroatom, ausgewählt aus N, O und S, wiedergibt, wobei der Ring gegebenenfalls an einen Benzolring oder einen 5- oder 6-gliedrigen, mindestens ein Heteroatom, ausgewählt aus N, O und S, enthaltenden, heterocyclischen Ring kondensiert ist, wobei das Ringsystem insgesamt, gegebenenfalls mit einer oder mehreren Gruppen, unabhängig ausgewählt aus OH, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Halogen und $NHSO_2(C_{1-4}$-Alkyl), substituiert ist, und wenn ein Glied des Ringsystems S darstellt, kann es mit einem oder zwei Sauerstoffatomen substituiert sein;
X CH oder N wiedergibt und
L nicht vorliegt,
oder eine cyclische Gruppe der Formel Ia wiedergibt,

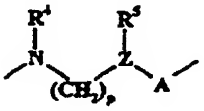


Ia

worin A an R^3 gebunden ist,

A CO oder SO_2 wiedergibt,
Z CH oder N wiedergibt,
m 1 oder 2 wiedergibt und zusätzlich, wenn Z CH wiedergibt, kann es 0 wiedergeben; und
n 1, 2 oder 3 wiedergibt, mit der Maßgabe, dass die Summe von m und n 2, 3, 4, oder 5 ist,

oder eine Kette der Formel Ib wiedergibt,



Ib

worin A an R^3 gebunden ist,
A und Z wie vorstehend definiert sind,
R^4 und R^5 unabhängig H oder C_{1-4}-Alkyl wiedergeben und
p 1, 2 oder 3 wiedergibt und zusätzlich, wenn Z CH wiedergibt, kann es 0 wiedergeben,

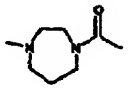
oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, worin R^1 Methoxy wiedergibt.

3. Verbindung nach Anspruch 1 oder Anspruch 2, worin R^2 Phenyl oder 2-Pyridinyl wiedergibt.

4. Verbindung nach einem vorangehenden Anspruch, worin R^3 Morpholinyl oder einen Piperidinring, der an einen Benzol- oder Pyridinring kondensiert ist, wiedergibt.

5. Verbindung nach einem vorangehenden Anspruch, worin L nicht vorliegt oder



wiedergibt.

6. Verbindung nach Anspruch 5, worin L nicht vorliegt und R^3 einen Piperidinring, kondensiert an einen Benzolring, der mit $NHSO_2(C_{1-4}$-Alkyl) substituiert ist, wiedergibt.

7. Pharmazeutische Formulierung, die eine Verbindung der Formel I, wie in Anspruch 1 definiert, oder ein pharmazeutisch verträgliches Salz davon in Anmischung mit einem pharmazeutisch verträglichen Hilfsstoff, Verdünnungsmittel oder Träger einschließt.

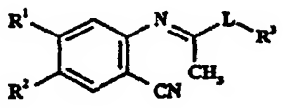
8. Verbindung der Formel I, wie in Anspruch 1 definiert, oder ein pharmazeutisch verträgliches Salz davon zur Verwendung als Pharmazeutikum.

9. Verwendung einer Verbindung der Formel I, wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon bei der Herstellung eines Arzneimittels zur Behandlung von gutartiger Prostatahyperplasie.

10. Verfahren zur Herstellung einer Verbindung der Formel I, wie in Anspruch 1 definiert, oder eines pharmazeutisch

verträglichen Salzes davon, das umfasst:

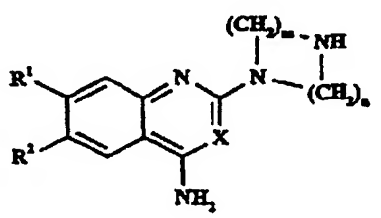
(a) wenn X CH wiedergibt, Cyclisieren einer Verbindung der Formel II



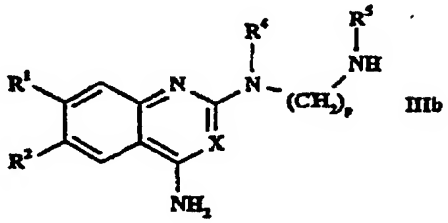
II

worin R^{1-3} und L wie in Anspruch 1 definiert sind; oder

(b) wenn Z N wiedergibt, Umsetzen einer Verbindung der Formel IIIa oder IIIb, falls geeignet,



IIIa



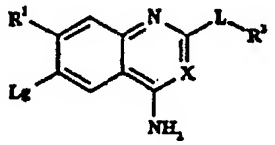
IIIb

worin R^1, R^2, R^4, R^5, X, m, n und p wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel IV

$$Lg\text{-}A\text{-}R^3 \qquad IV$$

worin R^3 wie in Anspruch 1 definiert ist, A CO oder SO_2 wiedergibt und Lg eine Abgangsgruppe wiedergibt, oder

(c) Umsetzen einer Verbindung der Formel V



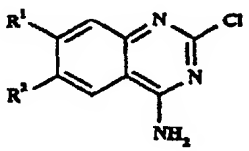
V

worin R^1, R^3, X und L wie in Anspruch 1 definiert sind und Lg eine Abgangsgruppe darstellt, mit einer Verbindung der Formel VI

$$R^2\text{-}M \qquad VI$$

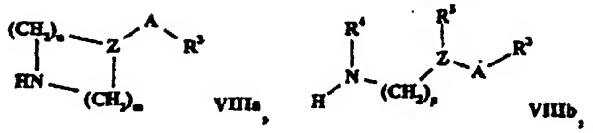
worin R^2 wie in Anspruch 1 definiert ist und M substituiertes Bor, Zink oder Zinn wiedergibt, in Gegenwart eines Palladiumkatalysators, oder

(d) wenn X N wiedergibt, Umsetzen einer Verbindung der Formel VII



VII

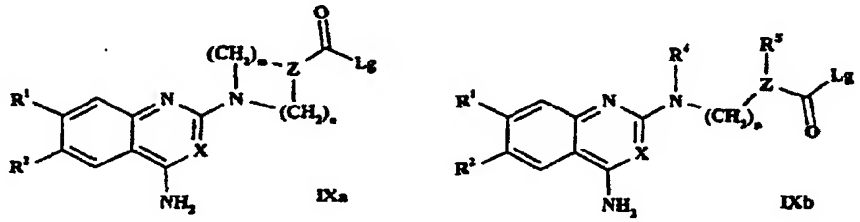
worin R^1 und R^2 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel VIIIa, VIIIb oder VIIIc, falls geeignet,



VIIIa, VIIIb,

HR^{3a} VIIIc worin R^{3-5}, A, Z, m, n und p wie in Anspruch 1 definiert sind und R^{3a} die gleiche Bedeutung wie R^3 in Anspruch 1 aufweist, mit der Ausnahme, dass es ein nucleophiles Stickstoffatom in dem heterocyclischen Ring, welcher an das H in Formel VIIIc gebunden ist, enthält oder

(e) wenn A CO wiedergibt und R^3 ein nucleophiles Stickstoffatom in dem an L gebundenen heterocyclischen Ring umfasst, Umsetzen einer Verbindung der Formel IXa oder IXb, falls geeignet,



IXa IXb

worin R^1, R^2, R^4, R^5, X, Z, m, n und p wie in Anspruch 1 definiert sind und Lg eine Abgangsgruppe darstellt, mit einer wie vorstehend definierten Verbindung der Formel VIIIc, oder

(f) Umwandlung einer Verbindung der Formel I, worin L eine cyclische Gruppe der Formel Ia wiedergibt, zu einer entsprechenden Verbindung der Formel I, worin L eine Kette der Formel Ib wiedergibt, worin R^4 und R^5 jeweils H wiedergeben, durch die Wirkung einer starken Base, und, falls erwünscht oder erforderlich, Umwandeln der erhaltenen Verbindung der Formel I in ein pharmazeutisch verträgliches Salz oder umgekehrt.

11. Verbindungen der Formeln II, IIIa, IIIb und VII, wie in Anspruch 10 definiert.

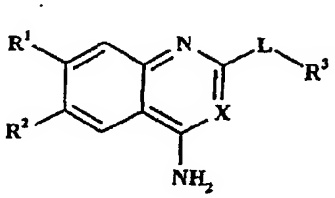
12. Verbindung der Formel V, wie in Anspruch 10 definiert, worin Lg die Triflatgruppe $-OSO_2CF_3$ wiedergibt.

13. Verbindung der Formel IXa, wie in Anspruch 10 definiert, worin Lg Chlor wiedergibt.

14. Verbindung der Formel IXb, wie in Anspruch 10 definiert, worin Lg Chlor wiedergibt.

Revendications

1. Composé de formule I



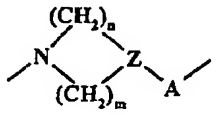
I

dans laquelle

R^1 représente alkoxy en C_{1-4} facultativement substitué par un ou plusieurs atomes de fluor ;

R^2 représente phényle, naphtyle, ou un hétérocyclique aromatique ayant 5 ou 6 chaînons, dont l'un au moins est N, O ou S, facultativement substitué par alkyle en C_{1-4} ou SO_2NH_2 ;
R^3 représente un noyau hétérocyclique à 4, 5, 6 ou 7 chaînons contenant au moins un hétéroatome sélectionné parmi N, O et S, le noyau étant facultativement fusionné à un noyau benzène ou à un noyau hétérocyclique à 5 ou 6 chaînons contenant au moins un hétéroatome sélectionné parmi N, O et S, le système cyclique, dans son entier, étant facultativement substitué par un ou plusieurs groupes indépendamment sélectionnés parmi OH, alkyle en C_{1-4}, alkoxy en C_{1-4}, halogéno et $NHSO_2$ (alkyle en C_{1-4}) et, lorsque S est un élément du système cyclique, il peut être substitué par un ou deux atomes d'oxygène ;
X représente CH ou N ; et
L est absent

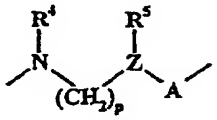
ou représente un groupe cyclique de formule Ia,



Ia

dans laquelle A est fixé à R^3 ;
A représente CO ou SO_2 ;
Z représente CH ou N
m représente 1 ou 2 et, en outre, lorsque Z représente CH, m peut représenter 0 ; et
n représente 1, 2 ou 3, pour autant que la somme de M et n soit 2, 3, 4 ou 5 ;

ou représente une chaîne de formule Ib,



Ib

dans laquelle A est fixé à R^3 ;
A et Z sont tels que définis ci-dessus ;
R^4 et R^5 représentent indépendamment H ou alkyle en C_{1-4} ; et
p représente 1, 2 ou 3 et, en outre, lorsque Z représente CH, m peut représenter 0 ;

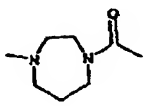
ou un sel pharmaceutiquement acceptable d'un tel composé.

2. Composé selon la revendication 1, dans lequel R^1 représente méthoxy.

3. Composé selon la revendication 1 ou la revendication 2, dans lequel R^2 représente phényle ou 2-pyridinyle.

4. Composé selon l'une quelconque des revendications précédentes, dans lequel R^3 représente morpholinyle, ou un noyau pipéridine qui est fusionné à un noyau benzène ou pyridine.

5. Composé selon l'une quelconque des revendications précédentes, dans lequel L est absent ou représente



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6. Composé selon la revendication 5, dans lequel L est absent et R^3 représente un noyau pipéridine fusionné à un noyau benzène qui est substitué par $NHSO_2$ (alkyle en C_{1-4}).

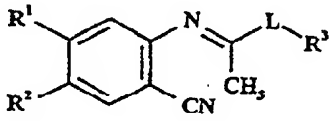
7. Formulation pharmaceutique incluant un composé de formule I, tel que défini dans la revendication 1, ou un sel pharmaceutiquement acceptable d'un tel composé, en mélange avec un adjuvant, diluant ou support pharmaceutiquement acceptable.

8. Composé de formule I, tel que défini dans la revendication 1, ou un sel pharmaceutiquement acceptable d'un tel composé, pour une utilisation comme produit pharmaceutique.

9. Utilisation d'un composé de formule I, tel que défini dans la revendication 1, ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans la fabrication d'un médicament pour le traitement de l'hyperplasie prostatique bénigne.

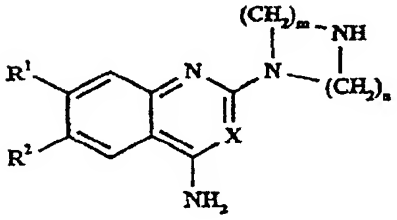
10. Procédé de production d'un composé de formule I, tel que défini dans la revendication 1, ou d'un sel pharmaceutiquement acceptable d'un tel composé, qui comprend :

(a) lorsque X représente CH, la cyclisation d'un composé de formule (II),

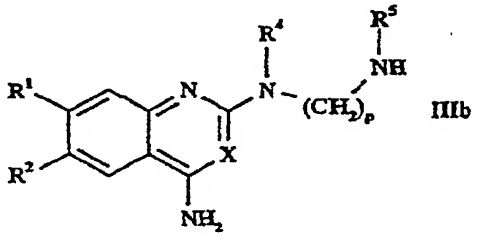


II

dans laquelle R^{1-3} et L sont tels que définis dans la revendication 1 ; ou
(b) lorsque Z représente N, la réaction d'un composé de formule IIIa ou IIIb, selon ce qui est approprié,



IIIa

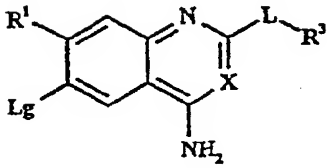


IIIb

dans lesquelles R^1, R^2, R^4, R^5, X, m, n et p sont tels que définis dans la revendication 1, avec un composé de formule IV,

$$Lg\text{-}A\text{-}R^3 \qquad IV$$

dans laquelle R^3 est tel que défini dans la revendication 1, A représente CO ou SO_2 et Lg représente un groupe labile ; ou
(c) la réaction d'un composé de formule (V)

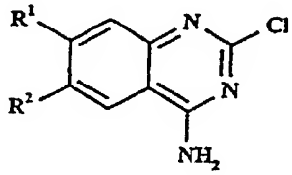


V

dans laquelle R^1, R^3, X et L sont tels que définis dans la revendication 1, et Lg est un groupe labile, avec un composé de formule VI,

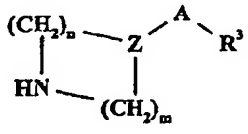
$$R^2\text{-}M \qquad VI$$

dans laquelle R^2 est tel que défini dans la revendication 1 et M représente du bore, du zinc ou de l'étain substitués en présence d'un catalyseur au palladium ; ou
(d) lorsque X représente N, la réaction d'un composé de formule VII,

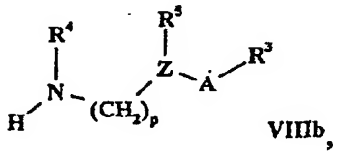


VII

dans laquelle R^1 et R^2 sont tels que définis dans la revendication 1, avec un composé de formules VIIIa, VIIIb ou VIIIc, selon ce qui est approprié,

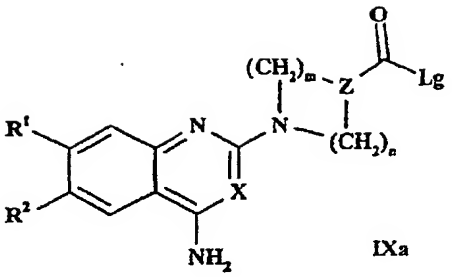


VIIIa,

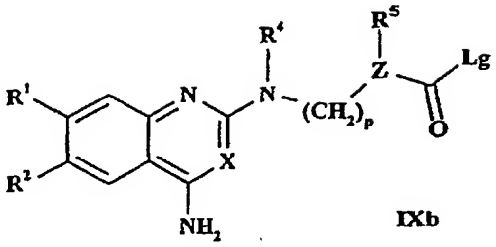


VIIIb,

HR^{3a} VIIIc dans lesquelles R^{3-5}, A, Z, m, n et p sont tels que définis dans la revendication 1, et R^{3a} a la même signification que R^3 dans la revendication 1, excepté qu'il contient un atome d'azote nucléophile dans le noyau hétérocyclique qui est fixé au H dans la formule VIIIc ; ou
(e) lorsque A représente CO et R^3 comprend un atome d'azote nucléophile dans le noyau hétérocyclique fixé à L, la réaction d'un composé de formule IXa ou IXb, selon ce qui est approprié,



IXa



IXb

dans lesquelles R^1, R^2, R^4, R^5, X, Z, m, n et p sont tels que définis dans la revendication 1, et Lg est un groupe labile, avec un composé de formule VIIIc tel que défini ci-dessus ; ou

f la transformation d'un composé de formule I dans lequel L représente un groupe cyclique de formule Ia en un composé correspondant de formule I dans lequel L représente une chaîne de formule Ib dans laquelle R^4 et R^5 représentent chacun H, par l'action d'une base forte ;

et, lorsque cela est souhaitable ou nécessaire, la transformation du composé résultant de formule I en un sel pharmaceutiquement acceptable ou vice versa.

11. Composés de formule II, IIIa, IIIb, et VII tels que définis dans la revendication 1.

12. Composé de formule V, tel que défini dans la revendication 10, dans lequel Lg représente le groupe triflate, $-OSO_2CF_3$.

13. Composé de formule IXa, tel que défini dans la revendication 10, dans lequel Lg représente chloro.

14. Composé de formule IXb, tel que défini dans la revendication 10, dans lequel Lg représente chloro.